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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,091	03/07/2008	Oliver Griesbeck	098832-0101	4598

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,091	GRIESBECK ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-60* is/are pending in the application.

4a) Of the above claim(s) *42-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks, filed on 28 April 2011.

Claim Status

Claims 27-60 are pending. Claims 39-40 are amended. Claims 1-26 are cancelled. However, claims 42-60 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 27-41 are under current examination.

Priority

This application claims benefit as a 371 of PCT/EP04/08739 (filed 08/04/2004) This application also claims benefit from EUROPEAN PATENT OFFICE (EPO) 03016691.2 (filed 08/04/2003). The instant application has been granted the benefit date, 4 August 2003, from the foreign application EPO 03016691.2

Species Election

The applicant has noted that some confusion occurred in the specification of a particular species (Remarks, riled 4/28/2011). Particularly, the applicant notes that SEQ ID NO:2 was misstated as being human troponin C, when in fact it was chicken troponin C. According to the applicant's species election (filed 12/6/2010), the applicant elected a species of chimeric protein comprising human troponin C. Accordingly, claims

requiring SEQ ID NO:2 (chicken troponin C) will be withdrawn as being drawn to non-elected species. Additional species will be rejoined at the time of allowance of a generic claim.

Claim Rejections - 35 USC § 112

The rejection of claims 39-40 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicants claim amendments. The applicant's claim amendments have been fully considered and are persuasive. The applicant has amended the claims to remove the indefiniteness. Therefore, the examiner hereby withdraws the rejection of claims 39-40 under 35 USC 112, 2nd paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Miyawaki et al. (US2003/0017538) in view of Gahlmann et al (Journal of Biological Chemistry. 1990; 265(21): 12520-12528) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues (Remarks, filed 4/28/2011, page 9, paragraph 3 through page 10, parag 2) that while Miyawaki teaches the genus of modified Ca2+-binding polypeptide comprising: a) a first chromophore of a donor-acceptor-pair for FRET (Fluorescence Resonance Energy Transfer); b) a Ca2+-binding polypeptide; and c) a second chromophore of a donor-acceptor-pair for FRET and Miyawaki further suggests the subgenus of a Ca2+-binding polypeptides comprising troponin C, the claimed species are non-obvious species of an obvious genus.

The applicant's basis for this argument is "the present inventors were the first to show, that unexpectedly, it is possible to create a calcium indicator that contains solely

a certain type of troponin C as calcium binding moiety and still responds very well to calcium stimuli" (Remarks, page 10, parag.2). This argument could be interpreted as being as assertion of there being a "lack of reasonable expectation of success" for creating a species of modified Ca2+-binding polypeptide comprising: a) a first chromophore of a donor-acceptor-pair for FRET (Fluorescence Resonance Energy Transfer); b) a Ca2+-binding polypeptide; and c) a second chromophore of a donor-acceptor-pair for FRET (as taught by Miyawaki), wherein the Ca2+-binding polypeptide is human troponin C, drosophila troponin C, or chicken troponin C. The applicant has provided no evidence that such a fusion protein would be difficult to make. Furthermore, the examiner asserted a "skilled artisan would have had a reasonable expectation of success in combining the teachings of Miyawaki et al. and Gahlmann et al. because the molecular biology required to substitute human troponin C for a generic troponin C was well established at the time of the instant invention" (Action, filed 12/29/2010, page 10). Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant argues that the "claimed invention...produced superior results when compared to the prior art" (Remarks, page 10, parag.4). The applicant's argument is unpersuasive, since the applicant is comparing the claimed fusion protein to a protein having a structure different from the one which is obvious over the combination of the cited art. The examiner supposes that the applicant is comparing the fusion protein of Miyawaki to the claimed invention. There is nothing of evidence that

the claimed invention is not suggested by the cited art and has a property which is unexpected from the combination of elements.

Furthermore, the applicant argues that the cited fails to provide any reason to use generic troponin C as the Ca^{2+}-binding polypeptide (Remarks, page 11, lines 5-6). Troponin C is well known in the art as a Ca^{2+}-binding polypeptide. As substitution of this particular Ca^{2+}-binding polypeptide for another would be an obvious variation to a skilled artisan. Miyawaki is such an artisan. Miyawaki demonstrates this by, in particular, disclosing the larger genus of modified Ca2+-binding polypeptides of which the applicant's invention is a species. Miyawaki particularly suggest troponin C as an example of Ca^{2+}-binding polypeptides which could be included in their invention (parag.0103). Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant offers no facts to suggest it is "doubtful where a single molecule of muscle troponin C would fold correctly and maintain its crucial capabilities for calcium-binding and conformational change in cytosolic environments" (Remarks, page 11, parag.4). Therefore the examiner views this merely as speculation by the applicant's representative. Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant further argues that knowledge of one skilled in the art would have taught away "from selecting troponin C as the Ca2+-binding polypeptide" (Remarks, page 12, parag.1). This is clearly refuted by the fact that an artisan (e.g., Miyawaki) skilled in the art of making modified Ca2+-binding polypeptides having a) a first chromophore of a donor-acceptor-pair for FRET (Fluorescence Resonance Energy Transfer); b) a Ca2+-binding polypeptide; and c) a second chromophore of a donor-

acceptor-pair for FRET clearly suggests "selecting troponin C as the Ca2+-binding polypeptide." Therefore, the examiner finds the applicant's argument unpersuasive.

The applicant suggests that there "was no reasonable expectation of success when the teachings of Miyawaki and Gahlmann" (Remarks, page 12, parag.2). Particularly, the applicant asserts that human troponin C would not demonstrate calcium-binding in a cytosolic environment (Remarks, page 13, parag.1). At the time of filing, skilled artisans understood the location of the calcium-binding domains in human troponin C. Therefore, a skilled artisan wishing to make a fusion protein having the calcium-binding domains of human troponin C would include the required calcium-binding domains regardless of where the fusion protein would be expressed. The applicant has provided no evidence that human troponin C would not demonstrate calcium-binding in a cytosolic environment. The examiner concludes this is merely attorney speculation. Therefore, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 27-41 under 35 U.S.C. 103(a) as being unpatentable over Miyawaki et al. (US2003/0017538) in view of Gahlmann et al (Journal of Biological Chemistry. 1990; 265(21): 12520-12528).

The examiner reiterates the pending rejection:

Claims 27-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyawaki et al. (US2003/0017538) in view of Gahlmann et al (Journal of Biological Chemistry. 1990; 265(21): 12520-12528).

Claim 27 is directed to a modified Ca2+-binding polypeptide comprising:

a) a first chromophore of a donor-acceptor-pair for FRET (Fluorescence Resonance Energy Transfer);

b) a Ca2+-binding polypeptide with an identity of at least 80% to a 30 amino acid long polypeptide sequence of human troponin C or chicken skeletal muscle troponin C or drosophila troponin C isoform 1; and

c) a second chromophore of a donor-acceptor-pair for FRET.

Miyawaki teaches Yellow Cameleon. Yellow Cameleon is a modified Ca^{2+}-binding (fusion) polypeptide comprising cyan fluorescent protein (CFP) + calmodulin + lysine linker + M13 + yellow fluorescent protein (YFP) useful for FRET (page 10, col. 2, lines 3-6, parag. 0154). Therefore, Miyawaki suggests the genus of modified Ca^{2+}-binding (fusion) polypeptides comprising a) a first chromophore of a donor-acceptor-pair for FRET; b) a Ca^{2+}-binding polypeptide; and c) a second chromophore of a donor-acceptor-pair for FRET. Furthermore, Miyawaki et al. suggest that similar fusion proteins having variety of different Ca^{2+}-binding polypeptides could be made and Miyawaki particularly suggest troponin C as an example of Ca^{2+}-binding polypeptides which could be included in their invention (parag.0103). Therefore, Miyawaki et al suggest: a modified Ca^{2+}-binding (fusion) polypeptide comprising cyan fluorescent protein (CFP) + troponin C + yellow fluorescent protein (YFP) useful for FRET.

Miyawaki fails to teach explicitly teach that the troponin C portion of the polypeptide of claim 27 is "human, chicken or Drosophila troponin C."

However, Miyawaki teach or suggest the limitations of dependent claims 28-34, because Miyawaki et al. suggest a FRET fusion protein having a donor/acceptor pair of CFP/YFP.

Regarding the limitations of claims 36-38 directed to fusion proteins further comprising localization signals, Miyawaki et al suggest these limitations (paragraphs 0075, 0095 and 0097).

Regarding the limitations of claims 39-40 directed to fusion proteins having certain functional characteristics, these do not further limit the structure of the claimed molecules. Therefore, they are intrinsic properties of the suggested fusion protein.

Regarding claim 39, the instant specification teaches that "the percent ratio change of a protein, the fluorescence emission intensities of the FRET donor and the acceptor were measured at their respective emission maxima" (page 32, lines 4-6). Miyawaki et al. teach measuring the emission spectra of yellow cameleon (parag.0027). Therefore, performing this measurement of the suggested fusion protein is obvious to one of skill in the art reading the cited art.

Regarding claim 40, Miyawaki does not present data which performs titration curves to generate the Kd (dissociation constant) for Ca2+ with the suggested fusion proteins. However, a skilled artisan studying measurements of intercellular calcium or monitoring calcium ion distribution would be interested in performing basic biochemical measurements on a newly made fusion protein. Therefore, making this measurement would be obvious to a skilled biochemist.

Gahlmann et al. teach the calcium-binding capacity of human troponin C. Therefore, Gahlmann also suggest the limitations of claim 35.

Regarding the limitations of claim 41, directed to specific SEQ ID NOs which represent the certain embodiments of the polypeptides of claim 29, the cited art has provided teachings and rationale for making a polypeptide having the breath of the instant claims. Therefore, the cited art suggests the species of chimeric protein comprising: (a) CFP as a first chromophore type; (b) human troponin C as a troponin type; and (c) YFP as a second chromophore type. The applicant was requested to indicate whether a SEQ ID NO can be used to identify the elected species. The applicant has failed to explicitly indicate which SEQ ID NO corresponds to the elected species. However, the specification indicates that SEQ ID NOs:3-4 comprise human cardiac skeletal muscle troponin C. However, since the species of claim 41 must contain the elements of claims 27-29, and these elements are suggested by the cited art, therefore, the specific SEQ ID NOs of claim 41 are suggested by the cited art.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a modified calcium-binding polypeptide comprising: (a) a first chromophor, (b) human troponin C, and (c) a second chromophor, having a FRET donor/acceptor pair.

Miyawaki et al. provides explicit teaching, suggestion and motivation to make a modified calcium-binding polypeptide comprising: (a) a first chromophor, (b) troponin, and (c) a second chromophor, having a FRET donor/acceptor pair.

The person of ordinary skill in the art would have been motivated to substitute

one known, equivalent element for another to obtain predictable results. The claimed fusion proteins would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant case, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute human troponin C for the generic troponin C teaching of Miyawaki in the FRET polypeptide suggested by Miyawaki in view of Gahlmann because human troponin C is an embodiment which would have utility in a system using human cells and would be functionally equivalent to the generic "troponin C." .

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Miyawaki et al. and Gahlmann et al. because the molecular biology required to substitute human troponin C for a generic troponin C was well established at the time of the instant invention.

Therefore the fusion proteins as taught by Miyawaki et al. in view of Gahlmann et al. would have been *prima facie* obvious over the fusion proteins of the instant application.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633